Randomized Controlled Trial of Resection Versus Radiotherapy after Induction Chemotherapy in Stage IIIA-N2 Non-small Cell Lung Cancer

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A recent article in the *Journal of the National Cancer Institute* presented results of the EORTC 08941 study.[1] The main conclusion was that surgical (i.e., chemotherapy and surgical resection) and non-surgical multimodality treatments (chemotherapy and radiotherapy) led to similar 5-year survival rates of approximately 15% among selected patients with stage IIIA-N2 non-small cell lung cancer (NSCLC) with response to induction chemotherapy.

This important study must be understood in its appropriate context of patients with unresectable IIIA-N2 disease: induction chemotherapy did not convert unresectable disease into resectable—as illustrated by the 50% incomplete resection rate in the surgery arm—and, not unexpectedly, did not result in better outcome compared with radiotherapy.

The crucial term "unresectable" was not clearly defined in the article. In the initial protocol (October 15, 1994), patients were eligible if "judged by the responsible surgeon to have irresectable N2-disease." This vital criterion was amended to the "guidelines for irresectability" as they are mentioned in the publication on page 443, by an amendment on September 15, 2000. Consequently, proper guidelines for irresectability were in place only in the final part of the recruitment (September 2000 until December 2002).

Another concern is how the assessment of irresectability was performed. This is a complex multidisciplinary process. This had to be "judged by an experienced thoracic surgeon," but there were 23 centers that randomized ≤1% of the patients. Was a multidisciplinary team with sufficient expertise in assessing resectability in N2 disease available?

Different European series with dedicated assessment of resectability point at remarkably similar 5-year survival rates of 36% (Swiss group),[2] 34% (Essen group),[3] or 30% (Leuven group)[4] among patients with IIIA-N2 disease with resection after induction treatment. Even if non randomized, all were well-designed prospective trials, with intent-to-treat reporting and reliable long-term follow-up. In the randomized US Intergroup data, 5-year survival again was 36%, if the mortality of pneumonectomy could be avoided.[5] The rationale of these studies is to provide surgery as the best local treatment for resectable NSCLC and improve outcome by induction therapy to manage distant micrometastasis. In this respect, it is noteworthy that, in the EORTC experience, surgery provided better local control (32% locoregional failure) than radiotherapy (55%).

The hypothesis of EORTC 08941 that surgery might improve the prognosis of unresectable N2 disease if performed after induction chemotherapy unfortunately did not become reality, so that chemoradiotherapy remains standard for this group. However, this should not lead to the over-interpretation this is the best choice for

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every patient with IIIA-N2 NSCLC. We concur with the editorial that patients who are good candidates for surgery may still be appropriately managed by using resection rather than radiation.[6] We should continue to pursue further improvement in the current 5-year survival prospects of approximately 30% with surgical multimodality treatment for resectable N2, by integration of modern techniques such as positron emission tomography-computed tomography, video-mediastinoscopy, and ultrasound-guided endoscopy into a truly multidisciplinary process of staging and assessment of resectability.[7,8] Furthermore, answers from ongoing trials on the question whether modern chemoradiotherapy induction may be superior to chemotherapy are eagerly awaited.

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